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# Near infrared spectroscopy to study the brain: an overview

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*This paper gives an overview of principles, technologies, and applications using near infrared spectrometry and imaging (NIRS and NIRI) to study brain function. The physical background is reviewed and technologies and their properties are discussed. Advantages and limitations of NIRI are described. The basic functional signals obtained by NIRI, the neuronal and the hemodynamic signal are described and in particular publications about the former are reviewed. Applications in adults and neonates are reviewed, too.*

**Keywords:** near infrared spectrometry, near infrared imaging, functional activation.

## 1. Physical consideration of near infrared spectroscopy and imaging

Near-infrared light penetrates tissue relatively deeply and easily passes through the skull and brain. To analyze brain function a sensor emitting near-infrared light is placed on the surface of the head and at a few centimetres distance the intensity of the reflected light is detected. This light intensity depends on the optical properties of the brain, e.g., if there is an increase in blood concentration in the brain, less light will pass and the intensity at the detector will be reduced. The changes associated with brain activity can non-invasively be detected using near-infrared spectrophotometry (NIRS) and imaging (NIRI).

Tissue can be optically characterized by two parameters, scattering and absorption. Absorption reduces the light transmission and constitutes a spectrum, which is a finger print of a specific substance. An important aim of NIRI is to interrogate deep layers of tissue. Below 650 nm oxyhemoglobin ($O_2Hb$) and deoxyhemoglobin (HHb) and above 950 nm water absorb strongly. Therefore, NIRI uses wavelengths between 650 nm and 950 nm, where light penetrates tissue relatively deeply and $O_2Hb$, HHb, cytochrome aa3, lipids and water show distinct spectra.

Characteristic for light propagation in tissues is the strong scattering. In the NIR range, the scattering coefficient is more than one order of magnitude higher than the absorption coefficient and light propagation is disordered after 1-mm path. Therefore, NIRI depends on adequate theoretical models, such as, e.g., the diffusion approximation to the Boltzmann transport equation for the semi-infinite boundary condition [1–8].

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The basic measuring scheme is the following. A light source is placed on the intact head. At a distance of 2–5 cm, a light detector receives the reemerging light. The photons travelling from source to detector penetrate several cm deep into tissue and contain the information about the brain [9–12].

For imaging applications, a mesh of sources and detectors is placed on the region of interest. The measured data is spatially reconstructed to obtain images of absorption and scattering. 2D (here called NIRI or optical imaging, also called optical topography or diffuse optical imaging) and 3D (optical tomography) images can thus be obtained (overview of the technical approaches in adults and neonates [13,14], summaries of functional imaging studies in adults [15–20]). Optical imaging is used by an increasing number of research groups [13]. It has proven to be advantageous compared to measurements on single locations, because changes can be localized and thus, measurements in single locations may not be representative for a larger volume of tissue, which is particularly true when functionally studying the brain. Online display of optical images visualizing $O_2Hb$ and HHb concentration with a time resolution of up to 6 Hz have been reported [21].

One major effort in the development of 3D optical tomography is the detection of cancer in the female breast [22–24]]. Time domain optical tomography was applied to study the head of neonates [13,14,25]. 3D optical tomography still has a low spatial resolution of 1 to 2 cm and requires 10 min of time to acquire an image [13] and was despite this limit recently used for a functional study [14,26]. However, the tomographic approach's time resolution severely limits its application for functional studies of the brain, but 2D optical imaging is feasible also for neuronal activity.

Fig. 1. Left: MCPII measuring system (bottom) and stimulation unit (top). Right: LEDs for visual stimulation (top right). The sensor contains 4 light sources (each with 730 nm and 830 nm LEDs) and 4 detectors (photodiodes), covering an area of 2.5 by 3.75 cm with 10 light bundles (bottom right).

Recently, we have built a continuous wave imaging device with a 100-Hz time resolution, which can measure parts of the brain [27]. This versatile, multi-channel NIRS instrument (Fig. 1) for the purpose of mapping brain activation in the neonatal and adult brain in response to motor, tactile, and visual stimulation. The optical linearity, stability, and high signal to noise ratio (> 70 dB) of the instrument were demonstrated using an *in vitro* validation procedure. It has 48 channels, 100-Hz time resolution and a dual 16-bit AD-converter. The set-up depends on the sensors used, typically it contains 4-light source location with 3 wavelengths of 730 nm, 800 nm, and 850 nm and 4 detector locations. This instrument has been miniaturized in the mean time and there is a wireless sensor available (Fig. 2).

NIRI currently has the following limitations:

- only the outer cortex (25 mm) can be investigated in adults, the head of neonates can be transilluminated, however. The skull is relatively transparent to near-infrared light,
- spatial resolution is limited (~10 mm), therefore usually no anatomical information is available,
- extracerebral blood flow may influence the results, special techniques (multidistance) remove this effect,

Fig. 2. Wireless NIRI instrument. The advantage of wireless technology is that it is more comfortable and less susceptible to movement articats, because there is no cable, which pulls the sensor. The device only weighs 40 g and the battery lasts for approximately 3 h.

- motion artifacts lead to changes in the signals and have to be eliminated.

NIRI has become a quickly growing method to study brain for the following reasons:

- NIRI quantifies important physiological measures, $O_2Hb$, HHb, tissue oxygenation, cytochrome aa3 (an enzyme of the respiration chain), $H_2O$ and lipids,
- the technique is non-invasive and painless,
- non-ionizing radiation is used,
- it can be used at the bedside,
- probes are attached relatively quickly to a subject,
- no sedation of the patients is required,
- NIRI measures continuously and displays results in real time,
- long term measurements are feasible (monitoring),
- NIRI is immune to electro-magnetic interference,
- NIRI is relatively inexpensive.

## 2. Brain studies by near-infrared imaging

One of the most important applications of NIRI is to functionally study activity of the brain and its development. Two major types of optical signals associated with brain activity can be detected by NIRI: The neuronal and the hemodynamic signal.

### 2.1. Neuronal signal

One potentially very interesting discovery is the detectability of the neuronal signal by NIRI, which is related to optical changes directly associated with neuronal activity. This signal arises within 100 ms after the onset of the stimulation and has been studied at the cellular level, in animal studies and in humans.

At the cellular level, it is, according to the literature, certain that the optical properties of neurons change depending on the activity. Several types of optical changes at the neuron have been suggested. Extensive reviews can be found in Refs. 15 and 28–31. Here is a short overview of the effects found.

Several authors have located optical changes in the neuronal membrane. Cohen [28] found voltage dependent changes in birefringence in the membrane of the axon of nerve cells. He suggested that the observed effect was either due to a thinning of the membrane or the Kerr effect. Stepnoski [32] observed a similar signal, which was practically simultaneous to the action potential. Tasaki [30] found that thermal (heat production and absorption), mechanical (swelling and shrinking) and optical (birefringence) changes in the axon were simultaneous and related to a sudden swelling of the gel layer of the membrane due to an increase in water content. This gel layer is superficial and about 0.5-μm thick and an integral part of the membrane of the axon.

Another type of optical change was located at the nerve terminal. Salzberg [33] studied the intact neurohypophysis of mice and reported large and rapid decreases in light scat-

 

tering, which accompanied the secretion by nerve terminals. These changes occurred in two phases and the fractional light intensity change was approximately 0.2%.

As a third type of signal, Cohen [28] reported a biphasic change in light scattering (90°), i.e., an increase in light scattering that was simultaneous to the action potential, after a return to the baseline another increase in light scattering was observed with a peak after 20 ms.

Sable [31] indicates other possible effects, such as cell swelling, changes in the cytoskeleton and changes in the geometry of microtubules, which change the light scattering of neuronal tissue.

In conclusion, there is extensive literature on studies in single neurons and brain slices, which demonstrates several effects as the origin of the neuronal signal at the neuronal level.

Further studies were performed on the exposed cortex in animals [31]. Grinvald [34] reported a decrease in reflected light 200 ms after the onset of whisker stimulation. Rector [35] found a similar response synchronous to the electrical signal. Malonek [36] reported an increase in light intensity with a latency (i.e., the period between stimulation and response) of 200 ms.

Rector [37] found four temporal components of the brain activity in rats. A weak response with a peak at 30 ms after the stimulus correlating with presynaptic activation was followed by an opposite and much larger signal at 80 ms. These two early responses were limited in their spatial distribution and were directly related to neural activity. The two slower components with peaks at 300 ms and 800 ms were spatially more extended and overlapped. The signal at 300 ms appeared to be consistent with the hemodynamic mapping signal described by Malonek [36], which is also called "the dip", i.e., a short increase in HHb at the onset of functional stimulation, which occurs before a marked decrease in HHb due to an increase in blood flow at 800 ms, which is the hemodynamic signal described in below. Thus, the neuronal signal is detectable in the exposed cortex.

Several research laboratories have therefore tried to detect the neuronal signal non-invasively in human subjects. The first attempt was published by Gratton in 1995. The group of Gratton continued to be productive in this field [38–51]. The reported neuronal signal is an increase in the phase of a frequency domain NIRI instrument.

The research group of the Berlin Neuroimaging Centre at the Charité was not able to reproduce the results of Gratton [52] (Please note that this paper is based on the first work of the Berlin Neuroimaging Centre and is therefore cited first. It was already presented at a conference in 1999 and suffered a delay in publication). Furthermore, Syré [52] performed Monte Carlo simulations to support their results and found that the expected change due to the neuronal signal was 0.01% in intensity or 0.01 ps time of flight (or 0.0004° in phase), which was much lower than the change reported by Gratton. The simulated change in time of flight was below the limit of detectability. From this simulation, it seemed to be more promising to study changes in intensity than in time of flight. Later indeed, a decrease in light intensity by 0.05% associated with neuronal activity was detected [53]. This signal was observed in 5 subjects. Movement artifacts were excluded, because the change was visible also when using median nerve stimulation below the motor threshold. Steinbrink [53] refers again to the Monte Carlo simulation and states, that the expected magnitude of the intensity change was 0.02%. Obrig [15] revealed that the Berlin Neuroimaging Centre no longer trusted its own results [53]. Since the signal was not found in the visual cortex or during stimulation below the motor threshold, the previous data were attributed to movement artifacts. Later, Steinbrink provided more details and confirmed that his previous results were due to movement artefacts [54]. No neuronal signal was found in the visual cortex. The findings of a new simulation were reported in addition. The maximum expected change was 0.01% in light intensity and 0.01 ps in time of flight, but more likely to be 0.0001%. This wide range of the simulated data shows that their Monte Carlo model is not reliable, because it depends on too many assumptions. This is not surprising since many factors are not precisely known. The conclusion was that it is not feasible to detect the neuronal signal non-invasively.

In our experiments [55–57], we found a mean change of light intensity of 0.0056% and 0.12 ps in time of flight (only one significant signal) in the motor cortex [55] during finger tapping and a mean change of light intensity of ~0.05% and no significant changes in time of flight in the visual cortex [56]. An independent component analysis was more sensitive to the neuronal signal, i.e., significant intensity changes were detected in 9 out of 14 subjects and were visible even in time frequency plots [57].

In order to distinguish neuronal signals from noise or artefacts, the following criteria were established.

The signal had to be:

- significantly different from noise ($p < 0.001$),
- related to the stimulation signal (tapping or reversing), i.e., disappears during rest periods,
- localized to exclude movement artifacts.

In addition there was good agreement between the latencies.

Franceschini [58] detected a change in intensity due to neuronal activity in 43% of the measurements during finger tapping, 60% during tactile stimulation and 23% during median nerve stimulation. The amplitude of the intensity change was ~0.1%. Franceschini only measured light intensity and not time of flight, but measured at two wavelengths. They also carried out numerical simulations. In addition, they further developed criteria to assess the robustness of the detected signal.

The signal had to be:

- similar between the two wavelengths,
- significantly different between stimulation and rest,
- similar between subsets of the data,
- lower in amplitude on the ipsilateral side compared to the contralateral side of the brain
- localized.

NIRI was compared to EEG by Medvedev in an object detection task using an independent component analysis. The good agreement is reported in Ref. 59.

A further group detected neuronal signals during a study on preattentive changes [60]. There are no reports on studies in neonates so far. Thus, it has not been tested, whether the neuronal signal is visible in neonates.

As it can be seen from this review of the literature, there is some controversy, whether the neuronal activity can be detected in non-invasively in adult human subjects. However, evidence accumulates that the neuronal signal can be detected. This may potentially be very exciting, because the neuronal signal is very likely to be more localized and thus, will deliver more precise information about activation and neurovascular coupling can be studied in more detail.

## 2.2. Hemodynamic signal

The hemodynamic signal is related to an increased blood perfusion in an area of activated neurons due to neurovascular coupling. Brain activity due to a specific stimulation leads to an increase in the local oxygen consumption immediately followed by an increase in blood flow [61], which in turn changes the oxygenation and hemoglobin concentrations, i.e., an increase in $O_2Hb$ and a decrease in HHb. These changes occur within a few seconds after the onset of the stimulation, are reproducible [62,63], highly localized [64] and have been extensively studied in adults [15–20,65].

There are few reports in the literature on hemodynamic effects in neonates, visual cortex [66–68], auditory cortex [69–72], speech frontal cortex [73], olfactory stimulation [74,75], pain [76–78], and motor cortex [14]. Bartocci's [75] findings during the presentation of unpleasant smells to infants are highly particular, because a decrease in $O_2Hb$ concentration was observed, while the HHb concentration remained approximately constant. This implies that the oxygenation of the brain dropped in the presence of an unpleasant odour. Kotilahti [72] found that the hemodynamic changes depend on the sleep state. The other studies can be summarized that as in adults, the $O_2Hb$ concentration increases a few seconds after the onset of the stimulation. A typical examples of an ensemble average is displayed in Fig. 3 [68]. In contrast to the findings in adults, the HHb concentration increases in the majority of the infants (90% in Ref. 79, 60.7% in Ref. 70, 61.5% in Ref. 71), no clear changes [69] or remains unchanged [72]. This may imply that the additional oxygen consumption due to neuronal activity is not compensated by the blood supply to the same degree as in adults. Furthermore, it clearly demonstrates that signals such as the BOLD signal, which exclusively reflect the HHb, are not sufficient to do functional studies in infants. Brain activity may be missed due to absent changes in HHb concentration, but could be detected by a method, which is sensitive to $O_2Hb$ concentration changes.

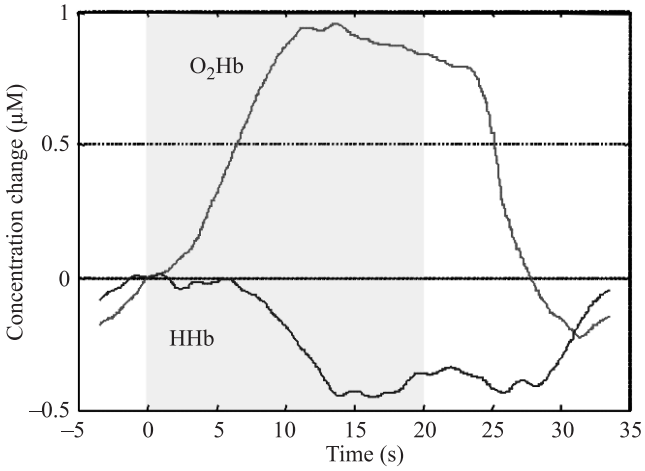


Fig. 3. The ensemble average of all significant hemdynamic responses ($O_2Hb$ and HHb) to stimulation in the visual cortex. After the onset of the stimulation $O_2Hb$ increases and the HHb decreases until both components reach a plateau. The end of the stimulation is followed by a decrease in $O_2Hb$ and an increase in HHb until they return to baseline. The decrease in HHb is approximately twice smaller than the increase in $O_2Hb$. There is a delay in the response of the HHb compared to the $O_2Hb$, which was not seen in adult subjects.

Optical imaging techniques in neonates clearly demonstrate a diagnostic potential [68,69,72,80–83], while optical tomography [14], although promising and fascinating, still needs development.

Chen [69] found that the auditory functional response of healthy infants (both $O_2Hb$ and total hemoglobin (tHb) increase) is highly significantly different from the one of infants suffering from hypoxic-ischemic encephalopathy (in a majority of the infants both $O_2Hb$ and tHb decrease). This paper clearly demonstrates the potential of NIRI to assess and understand the effects of brain injury and possibly predict outcome.

# 3. Conclusions

NIRI has been increasingly applied to study the brain and found to be reliable and reproducible in terms of hemodynamic effects associated with brain activity. Whether neuronal activity can be detected non-invasively is still somewhat controversial, although evidence in favour is accumulating. Due to its excellent properties for clinical applications, it is expected that the use NIRI in medicine will increase tremendously in the near future.

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